NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy [ID995]

Following release of the final appraisal determination (FAD), the company, Bristol-Myers Squibb, requested to submit an updated value proposition for nivolumab.

The following documents are made available to the consultees and commentators:

1. **Updated value proposition provided by the company**, Bristol-Myers Squibb

2. **Updated value proposition appendices provided by the company**, Bristol-Myers Squibb

3. **Review of the updated value proposition, provided by the Evidence Review Group,** Kleijnen Systematic Reviews

4. **Addendum, provided by the Evidence Review Group,** Kleijnen Systematic Reviews

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

BMS Proposal for Recommendation for use in the Cancer Drugs Fund for ID995:

Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy

Introduction

This document provides details of the commercial and data collection arrangement being proposed by BMS as part of this appraisal. This offering is designed to ensure that patients have access to this important new treatment whilst data can be collected which will address the Committee's concerns highlighted in the final appraisal determination. BMS recognise that as the clinical effectiveness data supporting this indication is from two single arm trials, there exists uncertainty in the estimated cost-effectiveness. By offering this commercial scheme, BMS are reducing this uncertainty and providing estimates of cost-effectiveness that are well below the end of life threshold, *even when incorporating the committee's preferred assumptions*. This should greatly reduce the risk to NICE and the NHS from approving this indication for use. Furthermore, the provision of four-year data for this indication will significantly reduce the uncertainty regarding the long-term efficacy of nivolumab and the simulated treatment comparison estimates, and provide a unique opportunity to characterise the long-term survival of nivolumab in this indication.

Revised commercial arrangement

BMS understand that the Appraisal Committee have concerns about the cost-effectiveness of nivolumab given the range of ICERs resulting from the different extrapolation methods used. Given the preference of the Committee to adopt the ERG's more conservative survival modelling approach and the uncertainty highlighted by the Committee due to the single-arm trial design, BMS are willing to offer a larger, confidential commercial discount to ensure that the ICER for nivolumab is *well below* the end of life threshold for cost-effectiveness. The commercial scheme will be administered directly with NHS England as a confidential rebate on the acquisition of nivolumab for patients with urothelial cancer after platinum-based chemotherapy.

In addition to the agreed NHS price reduction of [redacted]% for nivolumab in all indications, NHSE shall be entitled to receive a rebate of [redacted]% on the invoiced spend (equivalent to an overall discount of [redacted]% after VAT-adjustment) for the indication. The rebate will be based on the number of vials used for metastatic or unresectable urothelial cancer after platinum-based therapy in addition to the confidential NHS discount price. All rebates will include a VAT 'true-up' – calculation of this amount is provided below.

Table 1: Calculation of VAT 'true-up' for nivolumab for metastatic or unresectable urothelial cancer after platinum-based therapy using 4-ml vial

[redacted]

Abbreviations: BLC: baseline commissioning; CDF: Cancer Drugs Fund; VAT: value added tax.

Revised ICERs

The revised commercial proposal is based on the Committee's preferred economic assumptions, and presented versus paclitaxel, the UK standard of care in this setting. Multiple data sources have supported that paclitaxel is currently the most widely used treatment in this setting in the UK including; the SACT data[1]; the NICE clinical experts consulted during the appraisal[2]; an independently conducted physician survey done for the PLUTO trial[3] and a BMS-conducted chart review[4].

The ICERs for the current PAS and proposed commercial scheme, with the revised rebate applied for nivolumab, are presented in Table 2. All other model parameters and assumptions have remained unchanged to those that were presented by the ERG as part of the second Appraisal Committee Meeting on 23rd November 2017. Results are presented with a two-year treatment stopping rule under the assumption that any CDF agreement will include such a condition. This two-year treatment stopping rule has recently been implemented for other nivolumab indications approved for use in the CDF (namely squamous and non-squamous non-small cell lung cancer (TA483, TA484) and squamous cell carcinoma of the head and neck (TA490)). It has also been accepted as part of the ongoing appraisal for pembrolizumab as a treatment for locally advanced or metastatic urothelial carcinoma in adults who have had prior platinum-containing chemotherapy [ID1019]. For completeness, the same set of ICERs are presented in a scenario without a two-year treatment stopping rule.

Table 2: ERG scenario with 2-year treatment stopping rule (deterministic, nivolumab with PAS) adapted from Table 4: ERG Addendum "Nivolumab for treating metastatic or unresectable urothelial cancer: critique of BMS submission of November 9th 2017"

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Current baseline commission patient access scheme ([redacted])					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£42,480
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£57,253
Proposed CDF commercial scheme ([redacted])					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£36,217
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£48,953

Abbreviations: CDF: Cancer Drugs Fund; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PAS: patient access scheme.

Table 3: ERG revised base-case results without treatment stopping rule (deterministic, nivolumab with PAS) adapted from Table 3: ERG Addendum "Nivolumab for treating metastatic or unresectable urothelial cancer: critique of BMS submission of November 9th 2017"

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Current baseline commission patient access scheme ([redacted])					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£58,791
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£78,869
Proposed CDF commercial scheme ([redacted])					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£50,385
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£67,729

Abbreviations: CDF: Cancer Drugs Fund; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PAS: patient access scheme.

Impact of treatment waning effect post treatment stopping rule

To explore the impact of stopping the treatment effect for nivolumab, and to align with the sensitivity analysis provided as part of the ongoing appraisal *ID1019: pembrolizumab for urothelial cancer*, scenarios are presented whereby the treatment effect of nivolumab is removed after a specific time point. To implement this in the model, the time-varying hazard ratio for nivolumab versus the chosen comparator was set to 1 for any cycle, after the point of implementation, where it would otherwise have been >1. The waning effect is implemented after 3 years, 5 years and 10 years from starting treatment (i.e. 1, 3 and 8 years post stopping treatment with a two-year stopping rule). As can be seen below, this increases the ICERs slightly, but these remain below the decision-making threshold for all of the scenarios.

Please note that for ease of review, a table of the changes made to the model has been provided in Appendix B. This table documents all changes made to the model from the version that was submitted at the appraisal consultation stage (9th November 2017).

Table 4: ERG scenario with revised commercial scheme including treatment waning effect at varying time points

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
3 year waning effect					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,364	0.76	[redacted]	[redacted]	£40,153
Docetaxel	£13,762	0.88	[redacted]	[redacted]	£50,343
5 year waning effect					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,178	0.71	[redacted]	[redacted]	£37,020
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£48,953
10 year waning effect					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£36,219
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£48,953

Abbreviations: ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Results for taxanes

The final appraisal document highlights the Committee's concern regarding the discrepancy between the clinical outcomes from the economic model reported for paclitaxel and those reported for docetaxel. Specifically, the Committee understood from expert input in other ongoing immunotherapy appraisals, that both paclitaxel and docetaxel could be considered clinically equivalent and therefore inconsistencies in the direction of change in the ICERs confirmed its concerns about the validity of the company's economic model outputs. BMS would like to re-iterate that the reason for this discrepancy is due to the difference in trials that provided evidence for these two drugs and informed the evidence network analysis. BMS understand that this creates uncertainty for the committee regarding which values are the most appropriate estimation of clinical outcomes for the current UK standard of care (the taxanes) and whether the 'true' ICER lies closer to the value generated for paclitaxel or for docetaxel.

To reduce the uncertainty for the Committee, presented below is an overview of the total QALYs estimated for the combination of docetaxel/paclitaxel from the other ongoing appraisals that are being considered in this same indication (atezolizumab; ID1327, pembrolizumab; ID1019).

Table 5: Comparison of total QALYs for UK standard of care across all immunotherapy appraisals

	Atezolizumab (ID 1327)	Pembrolizumab (ID1019)	Nivolumab (ID995)
Total QALYs	**Taxanes: 0.57**	**UK SoC: 0.73**	**Paclitaxel: 0.69** **Docetaxel: 0.86**
Source	ERG critique of the company's updated analyses for second-line therapy from 13th November 2017, Table 17	ERG critique from 27th April 2017, Table 54*	Critique of BMS submission of November 9th 2017, Table 4

*updated ERG critique has not been published from the second appraisal committee meeting
Abbreviations: ERG: Evidence Review Group; QALY: quality-adjusted life year; SoC: standard of care.

The results from across these appraisals would indicate that the total QALYs for the current standard of care are more aligned with the estimates for paclitaxel (QALYs = 0.69) compared with the estimated QALYs for docetaxel (QALYs=0.86). Whilst there are some key limitations with this kind of comparison, it should, however, hopefully provide useful information to assist the committee in their decision making.

Unmet need in post-platinum urothelial cancer

There remains a significant unmet need for patients who have failed after platinum therapies. Neither of the other currently licensed immunotherapies have been recommended by NICE for this indication, leaving chemotherapy as the only treatment option for this patient group. The recently approved technology appraisal, TA492, for atezolizumab for untreated locally advanced or metastatic urothelial cancer when cisplatin is unsuitable, offers a treatment for patients but only when they are unsuitable for treatment with cisplatin. There remains a need for a more tolerable and efficacious treatment option for patients with this devastating disease.

Updated simulated treatment comparison and economic model results

As part of the appraisal consultation process, BMS submitted further data from the CheckMate 275 and CheckMate 032 trials that provided a further year of trial follow-up. Unfortunately, there was insufficient time to incorporate the additional data from the CheckMate 275 trial into the economic model and instead the summary results were presented it within the response document. Given the additional time, BMS have been able to update all the analyses (the prediction model, the simulated treatment comparison and the survival analysis) to incorporate the most recent CheckMate 275 and CheckMate 032 data. These results are provided in Appendix B and show that the additional information does improve both the results of the situated treatment comparison and the economic model, in favour of nivolumab.

Data collection proposal

1 Purpose of data collection proposal

The purpose of this data collection proposal is to outline how BMS propose to address the Committee's existing concerns with longer-term data from its existing clinical trial package for nivolumab.

2 Proposed commencement and period of agreement

This proposed data collection arrangement would take effect on publication of the managed access agreement. The data collection would be anticipated to conclude in December 2019, when it is expected that the 4-year follow-up data will be available from the CheckMate 275 and Checkmate 032 trials.

3 Anticipated patient eligibility

If nivolumab were recommended for use in the CDF, is it anticipated that key patient eligibility criteria for nivolumab's use in the Cancer Drugs Fund would be aligned to the studies supporting its use. These will be determined by NHS England in consultation with NICE and BMS.

4 Area(s) of clinical uncertainty

The long-term overall survival was a key area of uncertainty identified by the NICE committee. The primary source of data to address these will be the ongoing trial described under bullet 5 below.

5 Source(s) of data collection

Data collection from the ongoing clinical trials (CheckMate 275 and CheckMate 032) will be the primary source of data collection. A 4-year data cut from the CheckMate 275 trial is expected in October 2019. Table's 5 and 6 provides a brief description of the trial.

Clinical trial

As per the most recent database lock (June 2017 and October 2017), there are [redacted] patients in follow-up or still on treatment in the CheckMate 275 trial and [redacted] patients in follow-up or still on treatment in the CheckMate 032 trial. This gives a total sample size of [redacted] **patients** for whom BMS can continue to collect data for.

Table 6: CheckMate 275 overview

CheckMate 275 – Phase II study (n=270)
Description: Multicentre, open-label, single-arm phase II study, with nivolumab 3mg/kg Q2W via IV infusion over 60 minutes
Primary Endpoint: BIRC-assessed ORR
Secondary Endpoints: BIRC-assessed PFS, OS, investigator-assessed OR
Exploratory Endpoints: Investigator-assessed PFS, safety, HRQoL via the EORTC QLQ-C30 questionnaire, general health status via the EQ-5D-3L

Abbreviations: BIRC: blinded independent review committee, EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, EQ-5D-3L: EuroQoL 5-Dimensions 3-Levels, HRQoL: health-related quality of life; IV: intravenous, ORR: Overall Response Rate, OS: Overall Survival, PFS: Progression free survival, Q2W: every 2 weeks.

Table 7: CheckMate 032 overview

CheckMate 032 – Phase I/II study (n=78)
Description: Multicentre, open-label, multi-arm, phase I/II study, with nivolumab 3mg/kg Q2W via IV infusion over 60 minutes
Primary Endpoint: Investigator-assessed ORR
Secondary Endpoints: Investigator-assessed PFS, OS, DOR, Safety
Exploratory Endpoints: Assessed by PD-L1 expression (≥1% and <1%) ORR, OS and PFS, HRQoL via the EQ-5D and EQ-VAS questionnaires

Abbreviations: DOR: duration of response, EQ-5D: EuroQoL 5-Dimensions, EQ-VAS: EuroQol visual-analogue scale, HRQoL: health-related quality of life; IV: intravenous, ORR: Overall Response Rate, OS: Overall Survival, PFS: Progression free survival, Q2W: every 2 weeks.

SACT

5.1 The Systemic Anti-Cancer Therapy (SACT) dataset is a mandated dataset as part of the Health and Social Care Information Standards. Data can also be collected via the SACT dataset during the data collection arrangement period, specifically:

- Overall survival
- Duration of therapy

6 Outcome data to be collected

Clinical trial

6.1 The most pertinent outcome to be measured is long-term overall survival. At the end of the data collection period 4-year data shall be available from the ongoing CheckMate 275 and Checkmate 032 trials. This will be supplemented by the data collected in SACT.

SACT

6.2 Data collection via SACT will support data collected in the clinical trial. During the managed access agreement period, SACT will collect data on overall survival and duration of treatment.

7 Proposed data analysis plan

7.1 Analyses will be provided for nivolumab for previously treated urothelial cancer from the ongoing clinical trials and SACT.

References

1. National Institute for Health and Care Excellence. Clinical expert statement for ID995
2. Systemic Anticancer Therapy Dataset (SACT) 2015 Report. Top Regimens by Diagnostic Group – Urology (bladder)
3. Jones R, Hussain S, Protheroe A, Birtle A, Chakraborti P, Huddart R, et al. Randomized Phase II Study Investigating Pazopanib Versus Weekly Paclitaxel in Relapsed or Progressive Urothelial Cancer. Journal of Clinical Oncology. 2017;0(0):JCO.2016.70.7828.
4. Second-Line Treatment Patterns of Metastatic Urothelial Carcinoma in Europe. Clark O, Jaffe D, DeCongelio M, Li V W, Goulden S, Gooden K. https://abstracts.mirrorsmed.org/abstracts/second-line-treatment-patterns-metastatic-urothelial-carcinoma-europe

BMS Proposal for Recommendation for use in the Cancer Drugs Fund for ID995:

Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy

Appendix A: Updated Simulated treatment comparison results and economic model

The prediction model and simulated treatment comparison have been updated with the most recent data from CheckMate 032 (June 2017) and CheckMate 275 (October 2017), which provide the longest follow-up available for this indication. This section of the document details how this update was performed and provides the results obtained.

In addition, the survival analyses (progression-free survival, overall survival and time-to-treatment discontinuation) have been updated to incorporate the most recent CheckMate 032 and CheckMate 275 data from June and October 2017 respectively. The results have been updated in the economic model submitted by BMS in response to the appraisal consultation document (the model entitled 'ERG scenarios DEF 30082017KM [ACIC] BMS 091117'). Please note that a table summarising all the changes enacted to this model has been provided below in Appendix B.

Updated prediction models

The prediction models were updated with the latest data using the methodology outlined in Appendix D Section D.2.5.4 of the company submission ID995 dated 26th June 2017. All previously included trials were included again, and the only change was the use of the updated nivolumab data. The same covariates were chosen for inclusion in both the PFS and OS models, however, as expected, the covariate estimates changed (as shown in Table 1 and Table 2).

Table 1: PFS prediction model covariates in previous submission and updated model

	Previous		Updated	
Covariate	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Liver metastases	1.72 (1.32, 2.26)	<0.001	1.67 (1.28, 2.17)	<0.001
Visceral metastases	1.77 (1.23, 2.57)	0.002	1.63 (1.15, 2.31)	0.007
Age	0.99 (0.98, 1.00)	0.124	0.99 (0.98, 1.00)	0.247
ECOG PS (≥1)	1.20 (0.94, 1.53)	0.140	1.18 (0.94, 1.50)	0.158

Abbreviations: CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio.

Table 2: OS prediction model covariates in previous submission and updated model

	Previous		Updated	
Covariate	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Liver metastases	2.16 (1.60, 2.92)	<0.001	1.92 (1.44, 2.54)	<0.001
ECOG PS (≥1)	1.81 (1.36, 2.42)	<0.001	1.70 (1.30, 2.21)	<0.001
Visceral metastases	1.69 (1.03, 2.77)	0.038	1.91 (1.22, 2.97)	0.004
Haemoglobin (≥10 g/dL)	0.71 (0.50, 1.01)	0.056	0.76 (0.54, 1.05)	0.097

Abbreviations: CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio.

Updated simulated treatment comparison

The simulated treatment comparison (STC) was re-run using the methodology described in appendix D section D.2.5.5; the WinBUGS code used was that provided as part of the response to the ERG's clarification questions. The only change to the STC was that the input data was changed to reflect the updated data and prediction model output.

The models, particularly for PFS, now appear to be more consistent across the choice of fractional polynomial parameter values than previously. The longer follow-up in the nivolumab data means that less extrapolation is required. Please note that the additional constant hazard ratio analysis, which was requested at clarification stage, has not been updated.

Progression free survival

The goodness of fit statistics for the fractional polynomials model are presented in Table 3.

Table 3: DIC values for progression-free survival fractional polynomial models (fixed and random effects)

Fractional polynomial model – fixed effects	DIC value	Fractional polynomial model – random effects	DIC value
1st order FP, p=0	698.36	1st order FP, p=0	697.79
1st order FP, p=1	778.40	1st order FP, p=1	778.22
2nd order FP, p1=0, p2=1	604.21	2nd order FP, p1=0, p2=1	604.37
2nd order FP, p1=0, p2=0	664.17	2nd order FP, p1=0, p2=0	664.02
2nd order FP, p1=1, p2=1	**487.53**	2nd order FP, p1=1, p2=1	487.93

Abbreviations: DIC: deviance information criterion; FP: fractional polynomial.

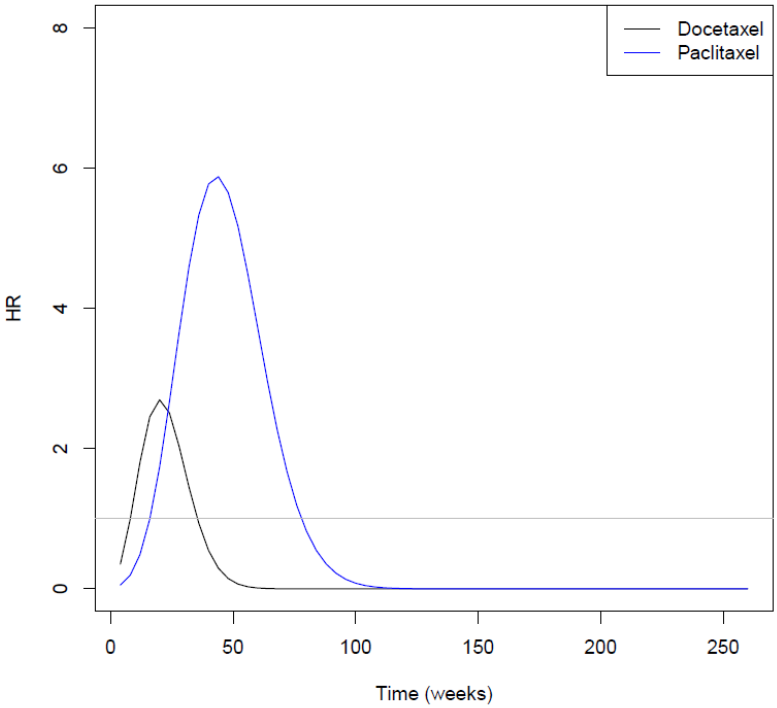
The second-order fractional polynomial model with fixed effects (p1=1, p2=1) is the best fitting according to the DIC value, followed closely by the second order (p1=1, p2=1) random effects model. The results from the fixed effects model p1=1, p2=1 are presented in the table below. All models have been updated in the economic model.

Table 4: Progression-free survival: network meta-analysis results (fixed effect second order (P1=1, P2=1) model): HRs and 95% credible intervals for each of the comparators versus nivolumab for selected time intervals

Comparison	Time interval (weeks)	HR (95% CrI)
Docetaxel versus nivolumab	0-4	0.35 (0.21, 0.56)
	8-12	1.80 (1.27, 2.50)
	20-24	2.51 (1.49, 3.92)
	44-48	0.15 (0.01, 2.33)
	68-72	0.00 (0.00, 0.42)
	92-96	0.00 (0.00, 0.03)
Paclitaxel versus nivolumab	0-4	0.06 (0.01, 0.15)
	8-12	0.49 (0.29, 0.78)
	20-24	2.66 (1.70, 4.06)
	44-48	5.65 (2.18, 11.59)
	68-72	1.67 (0.08, 15.43)
	92-96	0.14 (0.00, 11.79)

Abbreviations: CrI: credible interval; HR: hazard ratio.

Figure 1: Progression-free survival: network meta-analysis results (fixed effect second order (P1=1, P2=1) model): HRs for each of the comparators versus nivolumab



Abbreviations: HR: hazard ratio

Overall Survival

Table 5: DIC values for overall survival fractional polynomial models (fixed and random effects)

Fractional polynomial model – fixed effects	DIC value	Fractional polynomial model – random effects	DIC value
1st order FP, p=0	950.62	1st order FP, p=0	950.85
1st order FP, p=1	980.22	1st order FP, p=1	980.85
2nd order FP, p1=0, p2=1	899.01	2nd order FP, p1=0, p2=1	899.72
2nd order FP, p1=0, p2=0	931.52	2nd order FP, p1=0, p2=0	932.13
2nd order FP, p1=1, p2=1	837.40	2nd order FP, p1=1, p2=1	**836.66**

Abbreviations: DIC: deviance information criterion; FP: fractional polynomial.

The second-order fractional polynomial model with random effects (p1=1, p2=1) is the best fitting according to the DIC value, followed closely by the second order (p1=1, p2=1) fixed effects model. The results from the random effects model p1=1, p2=1 are presented in the table below. All models have been updated in the economic model.

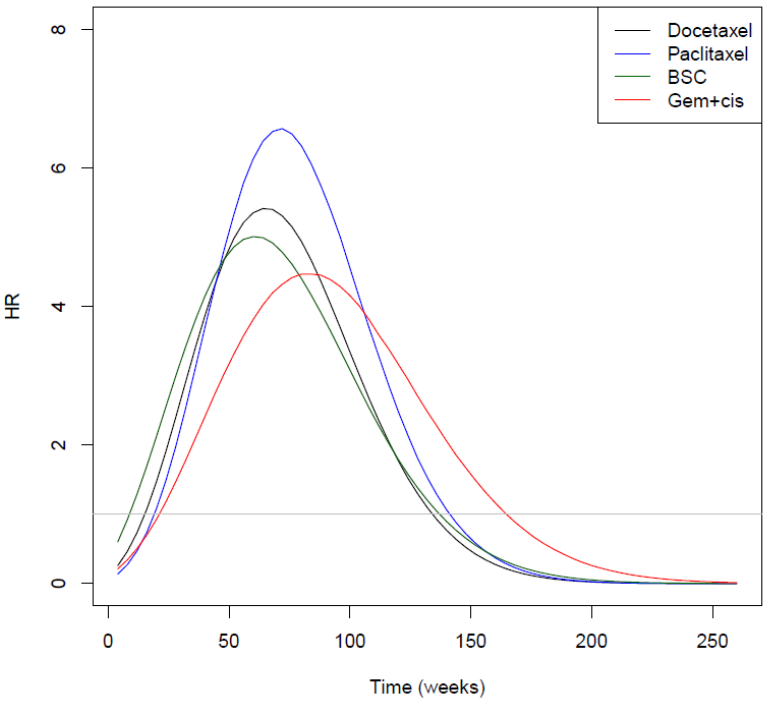
Table 6: Overall survival: network meta-analysis results (random effects second order (P1=1, P2=1) model): HRs and 95% credible intervals for each of the comparators versus nivolumab for selected time intervals

Comparison	Time interval (weeks)	HR (95% CrI)
BSC versus nivolumab	0-4	0.60 (0.08, 4.47)
	8-12	1.29 (0.18, 9.43)
	20-24	2.56 (0.36, 18.66)
	44-48	4.68 (0.65, 34.19)

	68-72	4.78 (0.66, 34.47)
	92-96	3.36 (0.46, 24.77)
Docetaxel versus nivolumab	0-4	0.26 (0.06, 1.09)
	8-12	0.74 (0.17, 2.92)
	20-24	1.92 (0.46, 7.56)
	44-48	4.67 (1.13, 18.85)
	68-72	5.31 (1.22, 22.69)
	92-96	3.70 (0.69, 18.50)
Paclitaxel versus nivolumab	0-4	0.14 (0.02, 1.18)
	8-12	0.47 (0.06, 3.63)
	20-24	1.50 (0.20, 11.35)
	44-48	4.82 (0.66, 36.19)
	68-72	6.57 (0.78, 53.66)
	92-96	5.00 (0.30, 76.87)
Cisplatin plus gemcitabine versus nivolumab (scenario analysis only)	0-4	0.21 (0.02, 1.81)
	8-12	0.51 (0.06, 3.73)
	20-24	1.19 (0.16, 8.52)
	44-48	3.03 (0.41, 21.73)
	68-72	4.32 (0.56, 30.65)
	92-96	4.29 (0.41, 36.72)

Abbreviations: BSC: best supportive care; CrI: credible intervals; HR: hazard ratio.

Figure 2: Overall survival: network meta-analysis results (random effects second order (P1=1, P2=1) model): HRs for each of the comparators versus nivolumab



Abbreviations: BSC: best supportive care, gem + cis: gemcitabine and cisplatin, HR: hazard ratio

Updated economic model results

With the additional follow-up and changing shape of the survival curves, the results are improved in favour of nivolumab versus paclitaxel and docetaxel. The outcomes for both

taxanes are also more similar, which aligns with the committee's understanding that these drugs are somewhat equivocal in clinical practice.

The improved cost-effectiveness results for nivolumab are in keeping with long-term evidence presented in other tumours, which have demonstrated a plateauing of the survival curves, due to the durable survival benefit seen with nivolumab.

Table 7: ERG scenario with 2-year treatment stopping rule (deterministic) and model updated to using latest CheckMate 032 and CheckMate 275 data

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Current baseline commission patient access scheme ([redacted])					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£12,960	0.37	[redacted]	[redacted]	£28,179
Docetaxel	£10,000	0.40	[redacted]	[redacted]	£31,702
Proposed CDF commercial scheme ([redacted])					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£12,960	0.37	[redacted]	[redacted]	£24,208
Docetaxel	£10,000	0.40	[redacted]	[redacted]	£27,623

Abbreviations: CDF: Cancer Drugs Fund; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 8: ERG revised base-case results without treatment stopping rule (deterministic) and model updated to using latest CheckMate 032 and CheckMate 275 data

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus nivolumab (£/QALY)
Current baseline commission patient access scheme ([redacted])					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£12,960	0.37	[redacted]	[redacted]	£38,291
Docetaxel	£10,000	0.40	[redacted]	[redacted]	£42,086
Proposed CDF commercial scheme ([redacted])					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£12,960	0.37	[redacted]	[redacted]	£32,990
Docetaxel	£10,000	0.40	[redacted]	[redacted]	£36,643

Abbreviations: CDF: Cancer Drugs Fund; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Impact of treatment waning effect

As in **Error! Reference source not found.**, the impact of a treatment waning effect at 3, 5 and 10 years is explored in the economic model.

Table 9: ERG assumptions with updated analysis and revised commercial scheme

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus nivolumab (£/QALY)
3 year waning effect					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£12,960	0.37	[redacted]	[redacted]	£24,208
Docetaxel	£10,040	0.40	[redacted]	[redacted]	£27,609
5 year waning effect					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£12,960	0.37	[redacted]	[redacted]	£24,208
Docetaxel	£10,009	0.40	[redacted]	[redacted]	£27,619
10 year waning effect					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£12,960	0.37	[redacted]	[redacted]	£24,208
Docetaxel	£10,000	0.40	[redacted]	[redacted]	£27,623

Abbreviations: ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Appendix B: Economic model changes

A small number of amendments have been made to the model submitted to NICE following the publication of the appraisal consultation document (the model entitled 'ERG scenarios DEF 30082017KM [ACIC] BMS 091117'). These amendments are summarised in Table 10.

Table 10: Summary of amendments to the economic model

Amendment number	Description	Cells amended in model
1	The ERG changes defined as 'matters of judgement' (no. 9 and 10) set to 1 to activate them.	ERG control sheet – cells D22:D23 (named "ERG_resp" and "ERG_miss")
2	Survival curve coefficients updated to include pooled analysis with latest data cut from CheckMate 032 and 275	'PFS & OS' sheet BP37:BT49 BP56:BT68 BP75:BT87 'Discontinuation' sheet AB27:AB39 BR48:BS60 BR65:BS77
3	The Cholesky decomposition matrices for PFS and OS have been updated so the probabilistic sensitivity analysis runs with the latest pooled data (as above).	'Chol Decomp – PFS' sheet All of the covariance matrices have been updated (cells B25:AZ40 [Weibull, Gompertz, Lognormal and Log-logistic], M5:S9 [exponential], BD28:BM46 [Generalised gamma]). 'Chol Decomp – OS' sheet All of the covariance matrices have been updated (cells B25:AZ40 [Weibull, Gompertz, Lognormal and Log-logistic], M5:S9 [exponential], BD28:BM46 [Generalised gamma]).
4	Reactivation of the treatment stopping rule functionality on the discontinuation sheet, so when the tickbox on the sheet is activated the discontinuation rule is implemented.	'Discontinuation' sheet – cells AH27:AH447
5	Addition of functionality on the 'PFS & OS' sheet to allow a treatment waning effect to be implemented (such that, after the time point the effect is implemented, the HR for the comparators is set to 1 for all cycles it would otherwise have been >1).	'PFS & OS' sheet H11:J12 (addition of functionality) F102:N381 (changes to model formulae) Q102:X381 (addition of extra cells to allow implementation of waning effect)

Amendment number	Description	Cells amended in model
6	Change to price discount	'Cost & Resource Use' sheet – cells F15:F16
7	The time-varying hazard ratios for all of the fractional polynomial models have been updated based on an analysis of the latest data cuts for the CheckMate - 275 and 032 studies.	'PFS & OS' sheet – cells E390:Y1248

Abbreviations: ERG: Evidence Review Group; HR: hazard ratio; PFS: progression-free survival; OS: overall survival.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Nivolumab for treating metastatic or unresectable urothelial cancer

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Authors	Nigel Armstrong, Health Economist, Kleijnen Systematic Reviews Ltd, UK Sabine Grimm, Health Economist, Maastricht UMC Bram Ramaekers, Health Economist, Maastricht UMC Xavier Pouwels, Health Economist, Maastricht UMC Shona Lang, Systematic Reviewer, KSR Ltd Debra Fayter, Systematic Reviewer, KSR Ltd Svenja Petersohn, Health Economist, Maastricht UMC Rob Riemsma, Reviews Manager, KSR Ltd Gill Worthy, Statistician, KSR Ltd Lisa Stirk, Information Specialist, KSR Ltd Janine Ross, Information Specialist, KSR Ltd Manuela Joore, Health Economist, Maastricht UMC Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University
Correspondence to	Nigel Armstrong, Kleijnen Systematic Reviews Unit 6, Escrick Business Park Riccall Road, Escrick York, UK YO19 6FD
Date completed	22/03/2018

Source of funding: This report was commissioned by the NIHR HTA Programme as project number STA 16/108/11.

Declared competing interests of the authors

None.

Acknowledgements

None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Armstrong N, Grimm S, Ramaekers BLT, Pouwels X, Lang S, Fayter D, Petersohn S, Riemsma R, Worthy G, Stirk L, Ross J, Joore MA, Kleijnen J. Nivolumab for treating metastatic or unresectable urothelial cancer: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2017.

Contributions of authors

Nigel Armstrong acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Xavier Pouwels and Svenja Petersohn acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter, Shona Lang and Rob Riemsma acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk and Janine Ross critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

Ab	Antibody
AE	Adverse Events
AIC	Akaike information criterion
ALT	Alanine transaminase
BI	Budget impact
BIC	Bayesian information criterion
BIRC	Blinded independent review committee
BNF	British National Formulary
BOR	best overall response
BSA	body surface area
BSC	Best supportive care
CDF	Cancer Drugs Fund
CD28	Cluster of differentiation 28
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIS	Carcinoma in situ
Cis	Cisplatin
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CHMP	Committee for Medicinal Products for Human Use
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events (NCI)
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
"D" ¯ "res"	Residual deviance
DIC ¯	Deviance information criteria
DOR	Duration of response
DSU	Decision Support Unit
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FDA	Food and Drug Administration
FP	Fractional polynomial
G-CSF	Granulocyte colony stimulating factor
GCP	Good Clinical Practice
Gem	Gemcitabine
GFR	Glomerular filtration rate
GP	General practitioner

HR	Hazard ratio
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
IC	Indirect Comparison
ICD	International Classification of Diseases
ICER	Incremental Cost Effectiveness Ratio
IFNγR	Interferon gamma receptor
IPD	Individual patient data
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to Treat
IV	Intravenous
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LPFT	Last patient first treatment
LYG	Life years gained
LYS	Life Year Saved
LYs	Life years
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare Products Regulatory Agency
MICE	Multiple imputation by chained equations
MRI	Magnetic resonance imaging
MVAC	Methotrexate, vinblastine, doxorubicin and cisplatin
NA	Not applicable
NCI	National Cancer Institute
NF-κB	Nuclear transcription factor-κB
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not Reached/Not Reported
NSCLC	Non-small cell lung cancer
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
pD	Number of effective parameters
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PH	Proportional hazards
PP	Post-progression
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PROs	Patient-reported outcomes
PS	Performance status
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
PSSRU HCHS	Personal and Social Services Research Unit Hospital and Community Health Services

PI3K	Phosphoinositide 3-kinase
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QALY(s)	Quality-adjusted Life Year(s)
QoL	Quality of life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Events
SD	Stable disease/Standard deviation
SE	Standard error
Shp-2	Src homology 2 domain-containing protein tyrosine phosphatase 2
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
STC	Simulated treatment comparison
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
TNM	Tumour-node-metastasis
TTD	Time to treatment discontinuation
TTR	Time to response
TURBT	Transurethral resection of the bladder tumour
UC	Urothelial carcinoma
UICC	Union for International Cancer Control
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VGPR	Very good partial response
WHO	World Health Organisation

Table of Contents

Table of Tables

Table of Figures

1. THE CDF PROPOSAL

In the latest submission by the company, a proposal for recommendation for use in the Cancer Drugs Fund for ID995, the company proposed a revised commercial arrangement that will be applied in addition to the agreed NHS price reduction of [redacted] % for nivolumab in all indications: a rebate of [redacted] % on the invoiced spend (equivalent to an overall discount of [redacted] %) for the indication.

The company presented revised ICERs claiming that these are based on the committee's preferences. The ERG's model settings have been maintained for the calculation of these ICERs. The company identified paclitaxel as the main comparator and justified this by citing opinion of NICE clinical experts during the appraisal,[8] the SACT data,[9] a physician survey and a BMS-conducted chart review. The company included only docetaxel as a further comparator and thereby excluded cisplatine+gemcitabine and Best Supportive Care (BSC). A 2-year treatment stopping rule was used in the company's new analysis, and the company justified this with the assumption that such a condition will be included in any CDF agreement, as well as with the implementation of such a stopping rule for nivolumab in other indications and the same stopping rule being accepted in the ongoing appraisal for pembrolizumab in the same indication. A scenario without this stopping rule was also provided. Furthermore, in an appendix, the company provided cost effectiveness results with the incorporation of more mature data from the CheckMate 032 (June 2017) and CheckMate 275 (October 2017) trials. Only with the 2-year stopping rule in place and if cisplatine+gemcitabine is not considered as comparator, the ICER for the comparison with paclitaxel drops below £50,000 per QALY gained (not taking the data update into account), and the ICER for the comparison with docetaxel remains above £50,000 per QALY gained. With the updated clinical effectiveness data, ICERs drop below £50,000 per QALY gained, but these model outcomes should be interpreted with caution.

2. NEW CLINICAL EFFECTIVENESS ESTIMATES

In their appendix, i.e. not in their main cost effectiveness analysis, the company provided cost-effectiveness results based on an updated simulated treatment comparison (STC).[1] The update is stated to be due to the incorporation of more mature data from the CheckMate 032 (June 2017) and CheckMate 275 (October 2017) trials. These data are reported in Appendix A to have informed an update in the survival analyses (progression-free survival, overall survival and time-to-treatment discontinuation).[2] All methods are stated to be those as described in the original CS.[3] The results used in the economic model were based on a selection of simulated treatment comparison (STC) model with the best model fit according to the deviance information criterion (DIC) value.

The company present a comparison between the original CS and the CDF proposal of the covariates in the prediction models by which adjustments are made to estimate the OS and PFS hazards for nivolumab as inputs in the STC.[2, 3] These are not reproduced in this report because it is unclear what the implications of any change on the STC might be. Suffice is to say that they are different as would be expected with updated survival data.

For OS, the company stated that the second-order fractional polynomial model with random effects (p1=1, p2=1) is the best fitting according to the DIC value. This contrasts with the original CS where the second order (P1=0, P2=0) fixed effect model was used in the base case in the cost effectiveness model analysis because it provided the most clinically plausible extrapolations out of the three best fitting models. Therefore, we present in Table 1 the results from both the CDF proposal and the CS.[2, 3] It should be noted that HRs greater than 1 favour nivolumab.

Table 1: Overall survival: STC results (CDF proposal vs. original CS): HRs and 95% credible intervals for each of the comparators versus nivolumab for selected time intervals

Comparison	Time Interval (weeks)	CDF HR (95% CrI)	CS HR (95% CrI)
Paclitaxel versus nivolumab	0-4	0.14 (0.02, 1.18)	0.13 (0.02–0.64)
	8-12	0.47 (0.06, 3.63)	0.69 (0.36–1.26)
	20-24	1.50 (0.20, 11.35)	1.43 (0.86–2.31)
	44-48	4.82 (0.66, 36.19)	2.27 (1.41–3.56)
	68-72	6.57 (0.78, 53.66)	2.63 (1.17–5.52)
	92-96	5.00 (0.30, 76.87)	2.75 (0.82–8.52)
Docetaxel versus nivolumab	0-4	0.26 (0.06, 1.09)	0.31 (0.09–0.84)
	8-12	0.74 (0.17, 2.92)	1.15 (0.75–1.72)
	20-24	1.92 (0.46, 7.56)	1.81 (1.25–2.62)
	44-48	4.67 (1.13, 18.85)	2.11 (1.46–3.00)
	68-72	5.31 (1.22, 22.69)	2.01 (1.14–3.37)
	92-96	3.70 (0.69, 18.50)	1.83 (0.8–3.87)
BSC versus nivolumab	0-4	0.60 (0.08, 4.47)	0.81 (0.33–1.79)
	8-12	1.29 (0.18, 9.43)	2.05 (1.36–3.08)
	20-24	2.56 (0.36, 18.66)	2.51 (1.69–3.72)
	44-48	4.68 (0.65, 34.19)	2.27 (1.57–3.25)
	68-72	4.78 (0.66, 34.47)	1.86 (1.17–2.85)
	92-96	3.36 (0.46, 24.77)	1.51 (0.82–2.66)
	0-4	0.21 (0.02, 1.81)	0.06 (0.00–0.70)

Cisplatin plus gemcitabine versus nivolumab (scenario analysis only)	8-12	0.51 (0.06, 3.73)	0.61 (0.21–1.37)
	20-24	1.19 (0.16, 8.52)	1.33 (0.66–2.49)
	44-48	3.03 (0.41, 21.73)	1.75 (0.96–2.99)
	68-72	4.32 (0.56, 30.65)	1.61 (0.68–3.31)
	92-96	4.29 (0.41, 36.72)	1.36 (0.37–4.05)
Source: Table 13 of CDF proposal and Table 18 of CS BSC = best supportive care; CrI = credible interval; HR = hazard ratio			

For PFS, the second-order fractional polynomial model with fixed effects (p1=1, p2=1) is the best fitting according to the DIC value in the CDF proposal, as opposed to the second order (P1=0, P2=0) fixed effect model as used for the base case analysis in the cost effectiveness model because it had clinical plausibility and the lowest DIC. No PFS data were available for cisplatin plus gemcitabine or BSC. Therefore, we present in Table 2 the results from both the CDF proposal and the CS.[2, 3] It should be noted that HRs greater than 1 favour nivolumab.

Table 2: Progression-free survival: STC results (CDF proposal vs. original CS): HRs and 95% credible intervals for each of the comparators versus nivolumab for selected time intervals

Comparison	Time Interval (weeks)	CDF HR (95% CrI)	CS HR (95% CrI)
Paclitaxel versus nivolumab	0-4	0.06 (0.01, 0.15)	0.07 (0.01, 0.36)
	8-12	0.49 (0.29, 0.78)	0.53 (0.30, 0.90)
	20-24	2.66 (1.70, 4.06)	1.63 (1.04, 2.52)
	44-48	5.65 (2.18, 11.59)	4.36 (1.84, 9.08)
	68-72	1.67 (0.08, 15.43)	7.26 (1.40, 28.85)
	92-96	0.14 (0.00, 11.79)	10.21 (0.91, 76.04)
Docetaxel versus nivolumab	0-4	0.35 (0.21, 0.56)	1.24 (0.61, 2.42)
	8-12	1.80 (1.27, 2.50)	1.72 (1.18, 2.49)
	20-24	2.51 (1.49, 3.92)	1.36 (0.78, 2.20)
	44-48	0.15 (0.01, 2.33)	0.75 (0.16, 3.19)
	68-72	0.00 (0.00, 0.42)	0.45 (0.04, 4.82)
	92-96	0.00 (0.00, 0.03)	0.29 (0.01, 6.93)
Source: Source: Table 11 of CDF proposal appendices and Table 20 of CS CrI = credible interval; HR = hazard ratio			

The company report that the models, particularly for PFS, now appear to be more consistent across the choice of fractional polynomial parameter values than previously and that the longer follow-up in the nivolumab data means that less extrapolation is required.

ERG comment

The ERG would accept that the polynomial fraction model appears to be a valid and highly flexible approach to estimating HRs. However, the results of very few functional forms continue to be presented, leaving some doubt as to the most appropriate. Also, one legitimate form is to assume proportional hazards i.e. a fixed HR with respect to time. This was done at the request of the ERG, although with some doubt as to the validity of the method and has not been conducted in the CDF proposal.[2, 4] Moreover, as shown in the tables above, the new sets of HRs appear to be substantially different to the

original CS ones. The company argue that there is more consistency across models, although no comparison of the resulting HRs has been presented. The ERG considers that such variation in HRs highlights the lack of reliability of the STC.

Since the same methods pertain to the CDF proposal, the ERG reiterates the other main limitations in the STC analysis:

1. Although the company stated that they had tested the fit of prediction models with various sets of baseline characteristics, it is not entirely clear how this was done: the final model had far fewer covariates than originally considered and no models with more covariates were presented or incorporated in the STC as part of a sensitivity analysis.
2. Many baseline characteristics were not available across all comparator trials and had to be imputed.
3. The only external test of validity of the STC i.e. the 'out-of-sample' method seemed to either show insufficient reduction in bias or be inapplicable given the use of the fractional polynomial model that was used for survival analysis.
4. To compound the uncertainty, the numbers of actual patients are small for all comparisons and not all studies provided data for all outcomes.
5. Not all study outcomes are based on independent review. An analysis based only on independent review derived data from the nivolumab trials was also requested.[5] However, in the response to the clarification letter, the company declined to do this.[6]

In conclusion, it continues to be difficult to be sure what the effectiveness of nivolumab is in comparison to the comparators in the scope. There is evidence from directly examining the single arms of the trial data that there is little difference between the outcomes measured from the nivolumab and comparator studies.[3] Of course, naïve comparison of single arms clearly carries a high risk of bias. However, there is also no clear evidence that this risk of bias would be reduced by the STC analysis. As stated on page 56 of TSD 18,[7] and used by the company for the basis of the STC: '*The size of this systematic error can certainly be reduced, and probably substantially, by appropriate use of MAIC or STC. Much of the literature on unanchored MAIC and STC acknowledges the possibility of residual bias due to unobserved prognostic variables and effect modifiers; however, it is not made clear that the accuracy of the resulting estimates is entirely unknown, because there is no analysis of the potential magnitude of residual bias, and hence no idea of the degree of error in the unanchored estimates. It is, of course, most unlikely that systematic error has been eliminated.'* The data informing the analysis from the CheckMate trials is more mature, but the limitation of the data from the comparator trials and the STC remain, as exemplified by the substantial change in the pattern of HRs for OS and PFS.

2. COST EFFECTIVENESS CONSIDERATIONS

Overall, the ERG was able to reproduce the company's results provided in their main CDF proposal document and appendices, with the exception of the treatment waning effect scenarios without the data update (the company only provided the treatment waning effect scenarios implemented in the model with the data update). The ERG would like to flag up a few points for consideration.

The economic model with the new data cut should not be used for decision-making

The company presented an updated cost effectiveness analysis with a new data cut only in their appendices, and not in the company's base-case.[2] The ERG previously noted that there was large uncertainty about overall survival (OS) and progression-free survival (PFS) for nivolumab and particularly surrounding the comparative treatment effectiveness, due to the availability of only a single-arm nivolumab study and the use of a STC.[10] As argued in the clinical effectiveness section of this document, the ERG would like to flag up that the use of the new data cut (including the updated STC) does not reduce uncertainty. If anything, uncertainty might be increased because the method for incorporating the new data cut and updated STC in the economic model is not well reported and the model predictions now lack face validity. The latter point is discussed in the following.

The updated STC is not presented as the company's base-case. However, when results of the updated STC are used, the ICERs of nivolumab compared with docetaxel and paclitaxel reduce significantly. The company explains that the additional follow-up and changing shape of survival curves (with the STC update) work in favour of nivolumab when compared with docetaxel and paclitaxel and that the outcomes for both taxanes are also more similar now, giving face validity to the new extrapolations. However, to the ERG it seems to be the case that the use of the data update in the model results in the comparator OS predictions significantly under-estimating the comparator observed OS and PFS data. This is illustrated for OS in Figures 1 to 4, which depict the OS predictions in the ACD response (Figures 1 and 3 for paclitaxel and docetaxel respectively) compared with the CDF proposal with the data update (Figures 2 and 4 for paclitaxel and docetaxel respectively). It can be seen that, whilst in the ACD response[11] the model predictions for paclitaxel and docetaxel make a reasonable fit to the observed KM estimates, the new model predictions based on the new data cut make a very poor fit. In particular, with the new data cut patients receiving paclitaxel or docetaxel die much sooner than what was observed in the respective studies. Because the nivolumab curve is not changed much, this results in much more favourable cost effectiveness estimates for nivolumab versus both paclitaxel and docetaxel. A similarly poor fit (based on visual inspection) can be observed for PFS in the CDF proposal with the data update.

The reason for this is unclear to the ERG. The company claim that they have updated the parameters for the curves. They do not explore different survival models and do not provide the statistical fit of these models to the data. This is one area of uncertainty and may contribute to a poor fit of predicted curves to the data.

The other change made by the company to incorporate the new data cut is the use of newly obtained hazard ratios (HRs) from the updated STC. As highlighted in the clinical effectiveness section of this document, the company finds HRs that are significantly different from the ones obtained in the original STC, and this may explain a difference in the fit of the model predictions to the data. Of course, it should also be acknowledged that the STC only uses a subset of the nivolumab data and that the resulting HRs therefore can result in predicted comparator curves deviating from the observed data. However, it is not clear to the ERG why this would have changed so significantly between the data used in the ACD response and the new data update in the CDF proposal, as the subset of the population used for the STC would remain unchanged.

It is for this reason that the ERG considers that the updated results should not be used for decision-making. In this context it is noteworthy that the company only provided the updated results in their appendices.

Figure 1. Overall survival nivolumab vs paclitaxel - ACD response

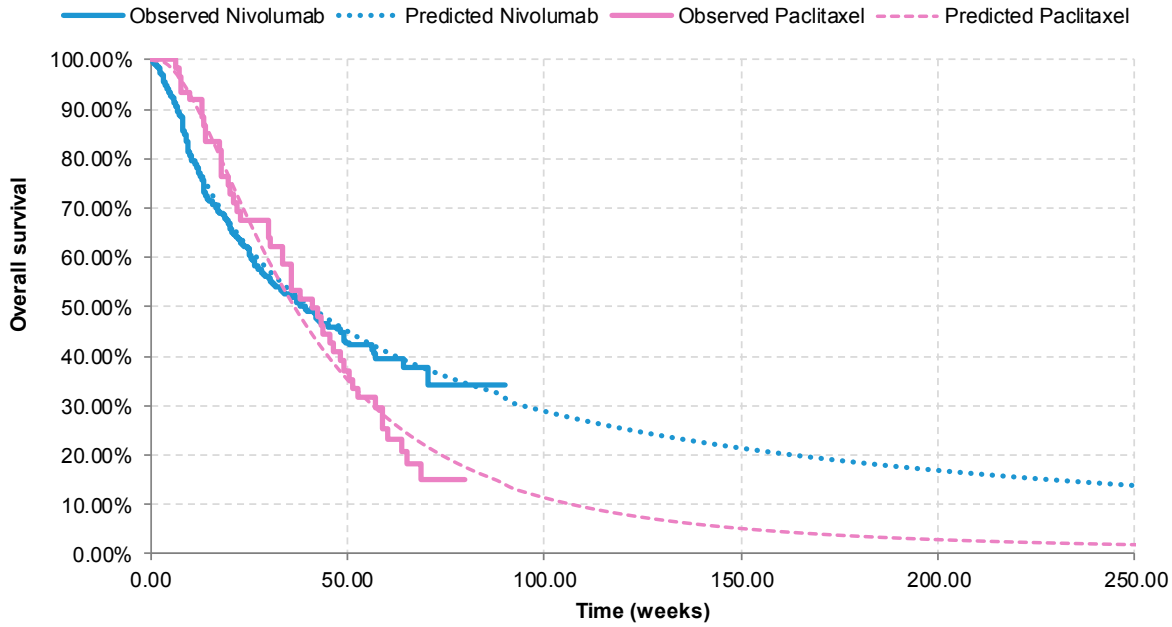


Figure 2. Overall survival nivolumab vs paclitaxel - CDF proposal with data update

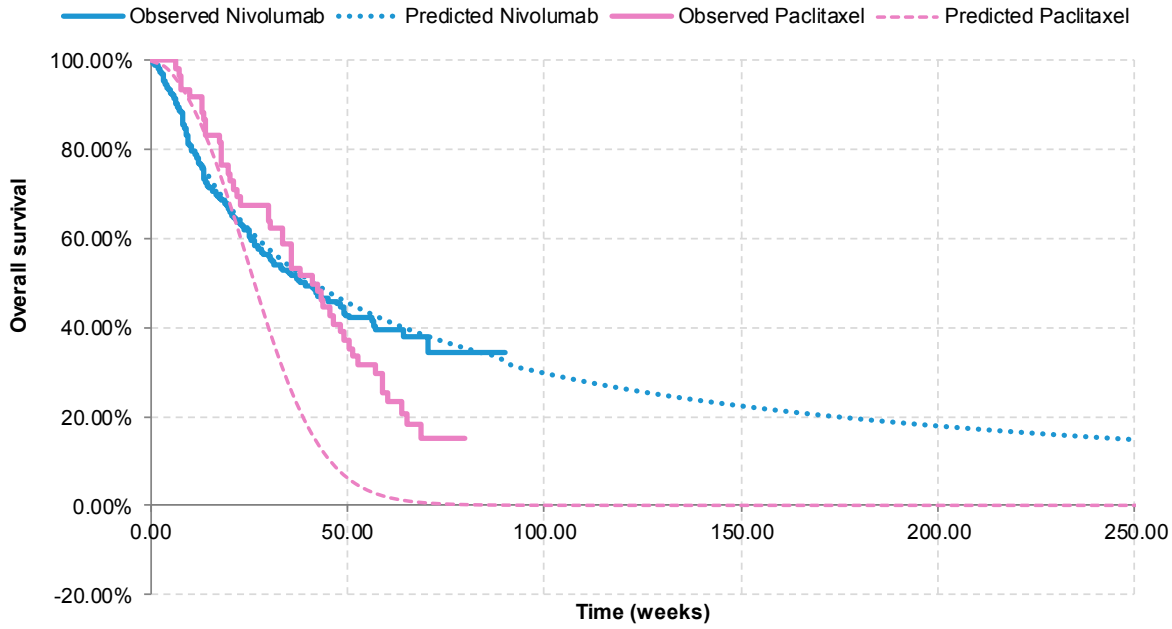


Figure 3. Overall survival nivolumab vs docetaxel - ACD response

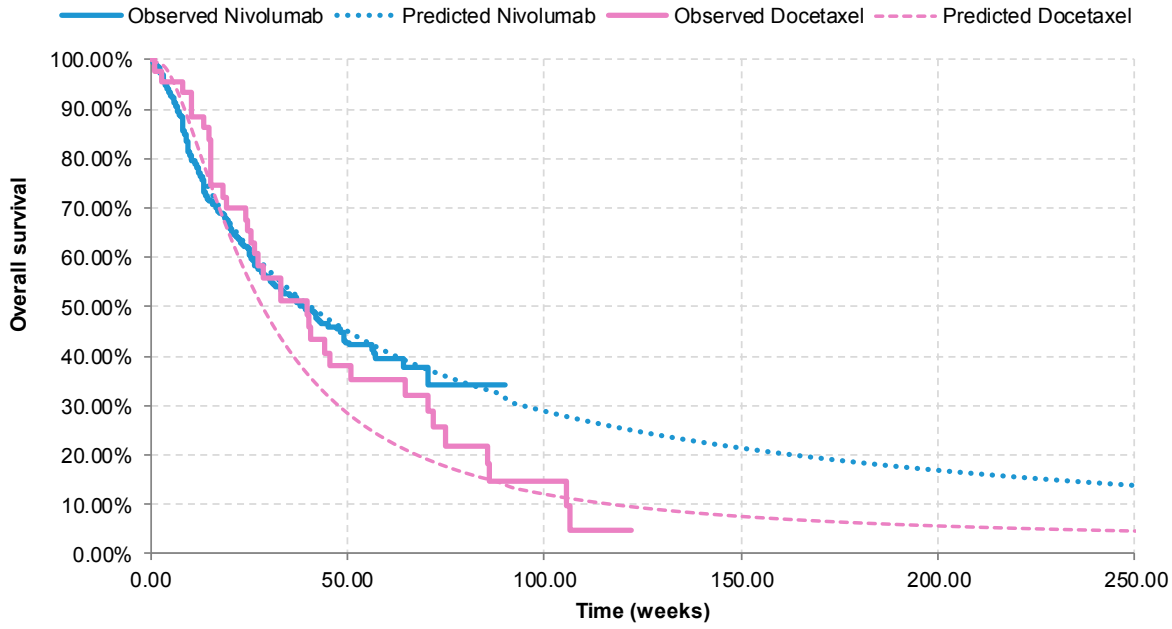
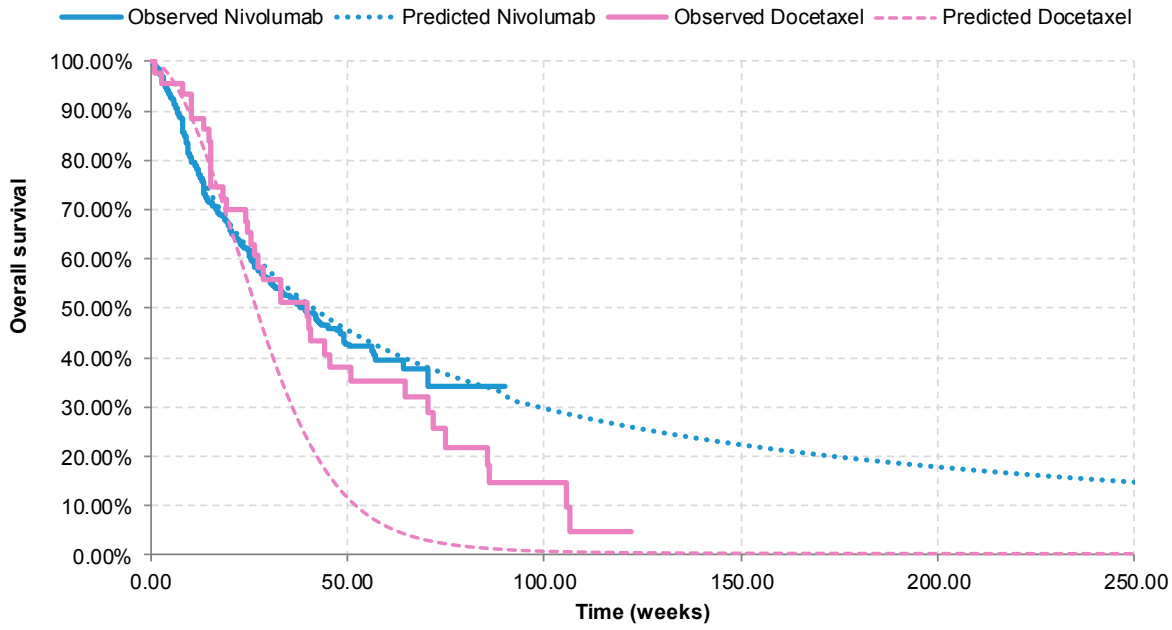


Figure 4. Overall survival nivolumab vs docetaxel - CDF proposal with data update



The 2-year stopping rule and treatment waning effect

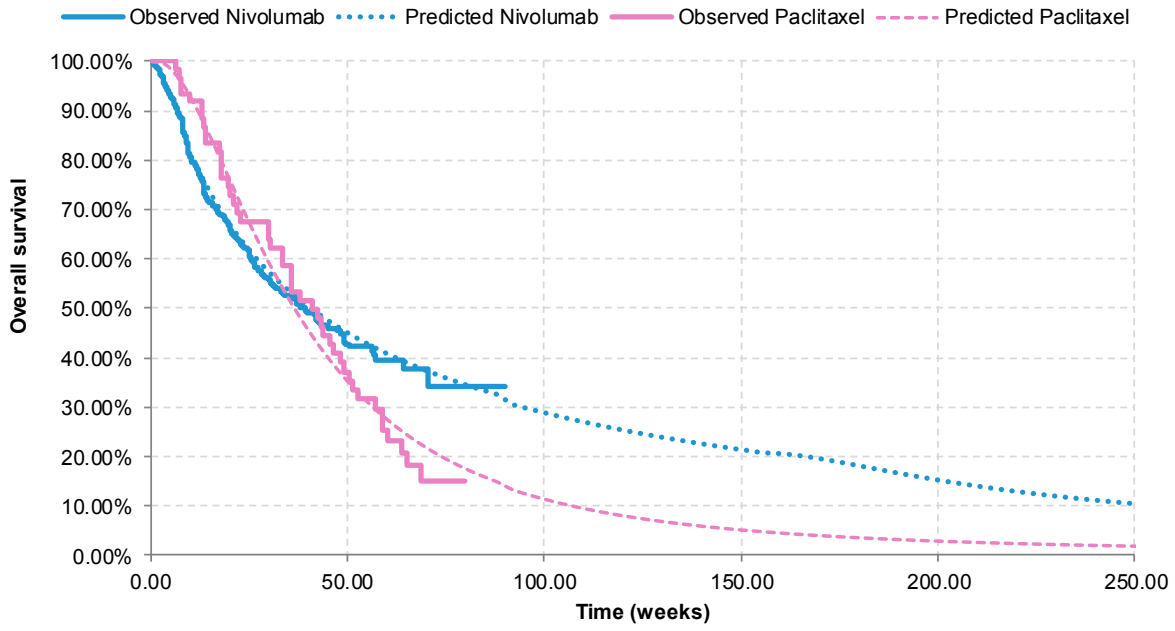
The company, in its new base-case, presents cost effectiveness with and without a 2-year treatment stopping rule in place. The ERG considers that the stopping rule scenario more appropriately reflects the cost of nivolumab during two years of CDF reimbursement. However, as previously noted by the ERG,[4] implementing a stopping rule focusing on treatment discontinuation only in the model would reduce the treatment costs while maintaining the effectiveness of continued treatment. Although it might be biologically plausible for treatment effects to continue after stopping treatment, the exact continued effect is uncertain.

For this reason, the company explored different time points for treatment waning effects after treatment discontinuation by setting the HR to 1 after these time points (3, 5, and 7 years). The impact on cost effectiveness results is significant in the model without the data update, but minimal in the model with the data update because even at only 2 years into the model time horizon, the proportion of patients treated with docetaxel and paclitaxel still alive is <1% (model with data update). This illustrates that the way the treatment waning effect is implemented may cause bias. Setting the HR to 1 at the specific time points results in the comparator curves to be adjusted to the nivolumab survival curves. However, the ERG considers that the waning *should* be reflected in an increased hazard of mortality or progression for nivolumab, thus altering nivolumab OS and PFS curves (instead of altering the OS and PFS curves for the comparators). It is also important to note that no evidence has been provided for the selected time points at which treatment waning is implemented in the model.

For these reasons, the ERG prefers to use no stopping rule in its base-case. However, acknowledging that this may over-estimate the cost of nivolumab when it is used for only 2 years within the CDF, the ERG explores an alternative approach for implementing a treatment waning effect to reflect the 2-year stopping rule in scenario analysis. In this alternative approach, the nivolumab survival curves are altered instead of the comparators' survival curves. This results in the nivolumab survival curve exhibiting a slight drop at the chosen time point, while the comparator curve remains unchanged (see Figure 5). The alteration of the nivolumab survival curves is realised by applying the docetaxel HRs (starting at period 1) to the 3-year time point. Using the docetaxel HRs may be considered to cause bias in favour of nivolumab because the patients who discontinue nivolumab may, in fact, move on to BSC, i.e. a less effective treatment. However, given the limitations around the BSC HRs (i.e. non-availability of HRs for PFS), the ERG preferred to use the docetaxel HRs in this scenario.

Conservatively, the ERG only explores the treatment waning effect starting at a 3-year time point. Even though there is no evidence for any time point, the ERG considered that 5 years may be over-estimating the time until the treatment waning would kick in, as this would entail 3 years of continued effectiveness as if patients had been treated while they were not. Given the significant uncertainty about treatment waning effects, the ERG prefers to use no stopping rule.

Figure 5. Overall survival nivolumab vs paclitaxel - tx waning effect at 3 years



ERG results

The ERG uses its ACD response model as the basis for the analysis, to avoid the use of the updated STC including the new data cut, which was associated with potential issues in the technical implementation and lacked face validity. This ACD response model is also the model version used by the company in their CDF proposal main document[1] and it produces the same ICERs to the company's when the same settings are used. The ERG prefers the no stopping rule scenario and therefore presents this as its base-case. Note that these results are the same as the company's results reported in their main CDF proposal document[1] Table 3.

In scenario analysis, the ERG explores the use of a stopping rule with the ERG method of implementing a treatment waning effect. The results (shown in Table 3) show that the ICERs decrease with the stopping rule in place, despite decreasing QALYs for the nivolumab treatment arm. Compared with the company's stopping rule and 3 year treatment waning effect scenario, the ICERs slightly increased for the comparison against paclitaxel (by about £1,000 per QALY gained) and significantly increased for the comparison against docetaxel (by about £8,000 per QALY gained).[1]

Due to the significant uncertainty in the comparative treatment effectiveness, the ERG considers it informative to present the naive treatment comparison without the new data cut in a scenario, with the updated price. The ICER in the comparison against paclitaxel decreases in this scenario compared with the ERG base-case and the ICER against docetaxel increases.

Table 3: ERG base-case and scenario analyses (with proposed CDF commercial scheme)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
ERG base-case: proposed CDF commercial scheme ([redacted]), no data update, no stopping rule*					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£50,385
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£67,729
ERG scenario 1: proposed CDF commercial scheme ([redacted]), no data update, 2-year stopping rule, ERG's treatment waning effect (at 3 years)					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£41,332
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£58,881
ERG scenario 2: Proposed CDF commercial scheme ([redacted]), naïve comparison, no data update, no stopping rule					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,064	0.65	[redacted]	[redacted]	£47,738
Docetaxel	£14,130	0.90	[redacted]	[redacted]	£71,274
* equivalent to company CDF response[1] Table 3					

3. CONCLUSIONS

The company claims that by offering this updated commercial scheme, the cost-effectiveness estimates for nivolumab are well below the end of life threshold. It should however be noted that this is only true if:

- The company's 2-year treatment stopping rule is adopted and;
- Gem+Cis is not considered as comparator.

As previously mentioned, it is unclear to the ERG why the 2-year stopping rule is appropriate in the current population. Moreover, implementing a stopping rule focusing on treatment discontinuation only would reduce the treatment costs while maintaining the effectiveness of continued treatment in the model. Although it might be biologically plausible for treatment effects to continue after stopping treatment, the exact continued effect is uncertain. Here the treatment waning effect scenarios might be informative; whenever implementing the treatment waning scenarios as preferred by the ERG, the ICERs for nivolumab versus docetaxel remain above £50,000 per QALY gained (despite the 2-year stopping rule being implemented) and only the ICER for nivolumab versus paclitaxel drops below that. In the ERG base-case, without the 2-year stopping rule, the ICERs for nivolumab versus paclitaxel and docetaxel are £50,385 and £67,729 respectively per QALY gained.

In conclusion, there remains substantial uncertainty about the ICERs generated (by both the company and the ERG). Uncertainties discussed in the ERG report, for example, the use of single arm studies to derive effectiveness and the method for the pooling of CheckMate 275 and 032 studies, remain unresolved. More uncertainty was introduced by the implementation of the updated data-cut in the health economic model (including the updated STC) which, according to the ERG should not be used for decision making. Furthermore, it should be noted that exploratory analyses in the original ERG report in an attempt at quantifying the impact of alternative assumptions had mostly an upward effect on the ICERs.

4. REFERENCES

[1] Bristol-Myers Squibb Pharmaceuticals Ltd. *BMS Proposal for Recommendation for use in the Cancer Drugs Fund for ID995: Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy*: Bristol-Myers Squibb, 2018. 8p.

[2] Bristol-Myers Squibb Pharmaceuticals Ltd. *BMS Proposal for Recommendation for use in the Cancer Drugs Fund for ID995: Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy. Appendix A: Updated simulated treatment comparison results and economic model* Bristol-Myers Squibb, 2018. 8p.

[3] Bristol-Myers Squibb Pharmaceuticals Ltd. *Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy [ID995]. Document B: Company evidence submission. Submission to National Institute of Health and Clinical Excellence. Single technology appraisal (STA)*: Bristol-Myers Squibb Pharmaceuticals Ltd, 2017. 143p.

[4] Kleijnen Systematic Reviews Ltd. *Nivolumab for treating metastatic or unresectable urothelial cancer: critique of BMS submission of November 9th 2017*. York, UK: Kleijnen Systematic Reviews Ltd., 2017. 10p.

[5] National Institute for Health and Care Excellence. *Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy [ID995]. Clarification letter*. London: NICE, 2017

[6] Bristol-Myers Squibb Pharmaceuticals Ltd. *Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy [ID995] – Response to request for clarification from the ERG*: Bristol-Myers Squibb Pharmaceutical Ltd, 2017. 97p.

[7] Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. *NICE DSU Technical Support Document 18: methods for population-adjusted indirect comparisons in submissions to NICE*. Sheffield: NICE Decision Support Unit, 2016. 81p.

[8] National Institute for Health and Care Excellence. *Technology Appraisal Committee Meeting (Committee D): 23 November 2017, 10.00-16.00*. Level 1A, City Tower, Piccadilly Plaza, Manchester: National Institute for Health and Care Excellence, 2017

[9] SACT. *Systemic Anticancer Therapy Dataset (SACT) 2015 Report. Top Regimens by Diagnostic Group – Urology (bladder) [Internet]*. Oxford: National Cancer Registration and Analysis Service, Public Health England, 2015 [accessed 22.3.18] Available from: http://www.chemodataset.nhs.uk/home

[10] Armstrong N, Grimm S, Ramaekers BLT, Pouwels X, Lang S, Fayter D, et al. *Nivolumab for treating metastatic or unresectable urothelial cancer: a Single Technology Assessment*. York: Kleijnen Systematic Reviews Ltd, 2017

[11] Bristol-Myers Squibb Pharmaceuticals Ltd. *Nivolumab for treating adults with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy [ID995] – company response to Appraisal Consultation Document (ACD)*. Middlesex: Bristol-Myers Squibb, 2017. 10p.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Nivolumab for treating metastatic or unresectable urothelial cancer

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Authors	Nigel Armstrong, Health Economist, Kleijnen Systematic Reviews Ltd, UK Sabine Grimm, Health Economist, Maastricht UMC Bram Ramaekers, Health Economist, Maastricht UMC Xavier Pouwels, Health Economist, Maastricht UMC Shona Lang, Systematic Reviewer, KSR Ltd Debra Fayter, Systematic Reviewer, KSR Ltd Svenja Petersohn, Health Economist, Maastricht UMC Rob Riemsma, Reviews Manager, KSR Ltd Gill Worthy, Statistician, KSR Ltd Lisa Stirk, Information Specialist, KSR Ltd Janine Ross, Information Specialist, KSR Ltd Manuela Joore, Health Economist, Maastricht UMC Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University
Correspondence to	Nigel Armstrong, Kleijnen Systematic Reviews Unit 6, Escrick Business Park Riccall Road, Escrick York, UK YO19 6FD
Date completed	28/03/2018

Source of funding: This report was commissioned by the NIHR HTA Programme as project number STA 16/108/11.

Declared competing interests of the authors

None.

Acknowledgements

None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Armstrong N, Grimm S, Ramaekers BLT, Pouwels X, Lang S, Fayter D, Petersohn S, Riemsma R, Worthy G, Stirk L, Ross J, Joore MA, Kleijnen J. Nivolumab for treating metastatic or unresectable urothelial cancer: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2017.

Contributions of authors

Nigel Armstrong acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Xavier Pouwels and Svenja Petersohn acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter, Shona Lang and Rob Riemsma acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk and Janine Ross critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

1. ADDENDUM TO ERG CRITIQUE OF THE COMPANY'S CDF PROPOSAL

The ERG wishes to reiterate that it considers that a stopping rule with treatment waning effect should not be used in the base-case, due to a lack of evidence on treatment effectiveness after treatment is discontinued. The ERG has also previously highlighted that the ERG's approach to implementing the treatment waning effect is conservative, given that it assumes docetaxel effectiveness after treatment discontinuation of nivolumab (and not BSC effectiveness). In the following tables, the ERG explored the impact of a treatment waning effect at 3, 5 and 10 years after starting treatment (assuming that treatment was stopped 2 years after starting). Table 1 presents these results using the previous ACM2 data, and Table 2 presents results using the updated STC. The latter should be interpreted with extreme caution, as the ERG's critique applies.

Table 1: ERG treatment waning effect scenario analyses (with proposed CDF commercial scheme)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
ERG scenario 1: proposed CDF commercial scheme ([redacted]), no data update, 2-year stopping rule, ERG's treatment waning effect (at 3 years)					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£41,332
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£58,881
ERG scenario 3: proposed CDF commercial scheme ([redacted]), no data update, 2-year stopping rule, ERG's treatment waning effect (at 5 years)					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£37,920
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£52,147
ERG scenario 4: proposed CDF commercial scheme ([redacted]), no data update, 2-year stopping rule, ERG's treatment waning effect (at 10 years)					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£36,662
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£49,777

Table 2: ERG treatment waning effect scenario analyses (with proposed CDF commercial scheme) with updated STC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
ERG scenario 5: proposed CDF commercial scheme ([redacted]), updated STC, 2-year stopping rule, ERG's treatment waning effect (at 3 years)					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£12,960	0.37	[redacted]	[redacted]	£34,566
Docetaxel	£10,000	0.40	[redacted]	[redacted]	£40,153
ERG scenario 6: proposed CDF commercial scheme ([redacted]), updated STC, 2-year stopping rule, ERG's treatment waning effect (at 5 years)					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£12,960	0.37	[redacted]	[redacted]	£29,230
Docetaxel	£10,000	0.40	[redacted]	[redacted]	£33,656
ERG scenario 7: proposed CDF commercial scheme ([redacted]), updated STC, 2-year stopping rule, ERG's treatment waning effect (at 10 years)					
Nivolumab	[redacted]	[redacted]			
Paclitaxel	£12,960	0.37	[redacted]	[redacted]	£25,492
Docetaxel	£10,000	0.40	[redacted]	[redacted]	£29,158